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# Mortality From Fungal Diseases in the US Air Force From 1970 to 2013

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## ABSTRACT

We review a unique set of documents, death certificates, catalogued in the US Air Force Mortality Registry, which tracks deaths for current and retired Air Force service members. We screened the records for all deaths caused by fungal diseases between 1970 and 2013. There were 216 deaths caused by a variety of diseases such as aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, pneumocystosis, sporotrichosis, and zygomycosis. The single most common identified cause of death was opportunistic candidiasis. Of the total 216 deaths, only 7 were active duty or active reserve personnel.

Fungal diseases rarely cause death in healthy young people. Both obligate parasitic fungi and opportunistic pathogens cause these diseases. Some military personnel are infected in their work environment with fungal pathogens such as the agents of histoplasmosis and coccidioidomycosis. Certain fungal diseases pose an increased threat to military personnel and retirees because of the frequency of serious wounds, amputations, and organ transplants compared to the overall civilian population. The Department of Veterans Affairs treats veterans and retirees for wounds and diseases acquired while in service.

There are ample reviews of historic disease trends in the US military; however, little comprehensive work has focused on all fungal deaths in the US Air Force (USAF).<sup>1</sup> Previous reviews of zoonotic disease morbidity in the USAF did not consider fungal disease zoonotic,<sup>2</sup> even if some derive from animal exposure. The US Air Force School of Aerospace Medicine maintains the Air Force Mortality Registry (AFMR). The AFMR is a unique resource that creates a database of all mortality data from death certificates, autopsy reports, etc, for active, reserve, and retired USAF service members to track trends and patterns that are more precise than Department of Defense casualty data. The AFMR tracks all causes of death including those from occupational and fungal diseases. We review those deaths in the context of historical disease significance and modern trends.

## MATERIALS AND METHODS

We queried 442,856 AFMR death records for all deaths after December 31, 1969, to December 31, 2012. The AFMR uses the *International Classification of Diseases-10th Revision* (ICD-10) codes to track causes of death. Death records were accessed when the ICD-10 code matched any of the following (or their subsections):

aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, pneumocystosis, sporotrichosis, zygomycosis, and unspecified mycosis. We analyzed each record. We further examined the death certificates which cite unspecified mycosis in an attempt to verify the fungal cause of death. We also examined death certificates in detail to verify place of death and other causes of death, if any. The death records included in this study were those of all individuals reported to have had a fungal disease as underlying cause of death. We used SAS 9.3 (SAS Institute Inc, Cary, NC) software for our analysis.

## RESULTS AND COMMENT

Overall, there were 216 deaths from fungal diseases from 1970-2012, summarized in the Table. There are limits to the data in the AFMR. Death records prior to the mid-1980s are sparsely represented and not all recent deaths have been documented, so records after 2010 could be underrepresented.

Pathogenic and parasitic fungi are ubiquitous but rarely cause death in the developed world. They are often associated with travel, the elderly, or a compromised immune system. Fatalities from fungal diseases are most often seen in the elderly as secondary infections, following organ transplants or chronic disease. Some fungi are legitimate parasites while others are only opportunistic environmental pathogens. We address each fungal pathogen alphabetically instead of following phylogenetic order.

**Aspergillosis:** *Aspergillus* spp are truly ubiquitous fungi with airborne conidia throughout the world.<sup>3</sup> They produce aflatoxins, but we did not consider any deaths related to these toxins. *Aspergillus* spp are saprophytic fungi, but aspergillosis threatens patients who

are immunocompromised, and fatal cases of aspergillosis increased after the introduction of corticosteroids and immunosuppressant drugs.<sup>4</sup> Aspergillosis is currently the leading cause of fungal deaths in the United States.<sup>3</sup> It was the second most common cause of death in the study, with 36 deaths. The first death recorded in the AFMR was in 1989. Sixty-one percent (n=22) of aspergillosis deaths were recorded from 2000 to 2012, with 1 and 13 deaths recorded for the 1980s and 1990s, respectively. We have not found a record of a female death thus far. The deceased were retirees, 55 years and older, the majority of whom died of pulmonary infections.

**Blastomycosis:** *Blastomyces dermatitidis* causes this relatively rare fungal disease. Most cases in the United States were acquired in the eastern half of the country, with a rate of approximately 2 per 100,000 people.<sup>5</sup>

This disease is relatively rare, with a low overall rate of mortality, but in some studies the death rate can exceed 12% in individuals over 65 years of age.<sup>5</sup> In the USAF, there were 4 deaths, all of which were retired males with either disseminated or unspecified infection sites. Four deaths were recorded from 1999 to 2003, with one death per year, 2001 being an exception. There were no records of death from blastomycosis after 2003.

**Candidiasis:** Numerous *Candida* spp cause candidiasis, with *Candida albicans* being the most frequently reported.<sup>6</sup> Disseminated or invasive candidiasis is one of the most prominent fungal causes of mortality in the United States. While invasive candidiasis is rare in people without risk factors, it is the fourth most common cause of hospital-acquired bloodstream infections in the United States.<sup>6</sup> Patients often acquire candidiasis following a traumatic injury or organ transplantation, or after suppression of the immune system due to age and/or other illness. Almost all of the 43 deaths (91%) recorded in the AFMR were men over the age of 60. While we are unable to know if they were suffering from underlying conditions, that is probable. A majority of cases (n=20 (46%)) were recorded from 2000-2012, preceded by 16 (37%) in the 1990s.

Characteristics of individuals with fungal cause of death listed for the period 1970-2012 (N=216) in the US Air Force Mortality Registry.

Variable	n	%N
<b>Gender</b>		
Male	211	97.69
Female	4	1.85
Unknown	1	0.46
<b>Age Group</b>		
20-44 years	18	8.33
45-54 years	16	7.41
55-69 years	50	23.15
65 years and older	135	61.11
<b>Race</b>		
White	167	77.31
Black	32	14.81
Hispanic	4	1.85
Unknown	13	6.02
<b>Underlying Cause of Death</b>		
Aspergillosis	36	16.67
Blastomycosis	4	1.85
Candida	43	19.91
Coccidioidomycosis	32	14.81
Cryptococcosis	12	5.56
Histoplasmosis	12	5.56
Mucormycosis/Zygomycosis	7	3.24
Pneumocystosis	25	11.57
Sporotrichosis	2	0.93
Unspecified mycosis	43	19.91
<b>Duty Status</b>		
Active Duty/Active Reserve	8	3.70
Retiree	208	96.29

**Coccidioidomycosis:** This disease is generally restricted to the western United States, where the causative agent *Coccidioides immitis* is endemic. It is an occupational hazard for military personnel training where soil is disrupted, such as on bombing ranges.<sup>7</sup> Coccidioidomycosis contributed the third highest number of fungal deaths during our study period. Coccidioidomycosis was one of the most significant fungal causes of death for USAF retirees, with 32 deaths. There is no way of knowing if they acquired the infections while on active duty. It also caused 3 deaths of active duty airmen, with a death in 1970, 1972, and 1992. Of these, approximately 75% died in western states, and the other cases could have been acquired there and reported at the site of death. Almost half of the deaths (n=15 (46%)), were recorded in the 1990s.

**Cryptococcosis:** Several *Cryptococcus* spp cause cryptococcosis. *Cryptococcus gattii* causes disease and is most common in immunocompetent people.<sup>8</sup> *Cryptococcus neoformans* is associated with animals and *Cryptococcus gattii* is more associated with certain trees and contaminated

habitats.<sup>8</sup> Both pathogens cause cryptococcosis and are reported identically in death records. The pathogens are regionally focal. Fatal cases of cryptococcosis often involve fungal meningitis.<sup>9</sup> Cryptococcosis is one of the most significant opportunistic infections for human immunodeficiency virus (HIV) patients, with an incidence rate of 0.04% to 12% worldwide, and up to 70% mortality.<sup>9</sup> The death of a 42-year-old male on active duty was recorded in 1985. All other cryptococcosis deaths were retirees. Ninety-one percent of the deceased were male, with one recorded as "null." Most cases were reported in the 1990s (41.67%), which might be related to the acquired immunodeficiency syndrome (AIDS) epidemic.

**Histoplasmosis:** Histoplasmosis is a disease caused by *Histoplasma capsulatum*. It is a dimorphic soil fungus (*Emmonsia capsulatum*) often associated with animal feces.<sup>10</sup> The parasitic form of histoplasmosis usually invades the lungs. Histoplasmosis is known to be one of the more common, yet very serious, fungal diseases in older Americans.<sup>11</sup> Histoplasmosis was considered

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among the top 3 fungal diseases among Medicare recipients, with the highest mortality.<sup>11</sup>

Within our study period, we record 12 fatalities from histoplasmosis. Ninety-one percent of the fatalities were male. A 25-year-old woman serving as a USAF reservist was among the fatalities for histoplasmosis, as well as a 37-year-old active duty Airman. These deaths occurred in 1990 and 1991, respectively. The remaining 10 were male retirees aged from 62 to 89 years. The deaths occurred from 1971 to 2007, with 3 deaths in 1993. Proportionate mortality ratios for histoplasmosis as 1.2 from 1970-2010<sup>1</sup>, indicating little to no difference between United States and Air Force proportionate mortalities. Hence, with the exception of the 2 individuals on active duty, the cases in retirees were predictable.

**Mucormycosis/Zygomycosis:** These diseases are caused by myriad species of Mucormycetes. We combined mucormycosis and zygomycosis deaths since they are both diseases caused by the same group of fungi. There are 7 records in the AFMR reporting mucormycosis/zygomycosis as the underlying cause of death. This is the second most common fungal disease in immunocompromised patients, but some opportunistic species infect immunocompetent hosts.<sup>12,13</sup> Unlike many of the fungal disease where a single or limited number of pathogens are known, mucormycosis is caused by a wide range of pathogens and thus has a wide geographic reach. A 27-year-old male active duty member was recorded with mucormycosis/zygomycosis as underlying cause of death. Seventy-one percent of cases occurred in the 1980s.

**Pneumocystosis:** Pneumocystosis is caused by *Pneumocystis jirovecii* or a related *Pneumocystis* spp.<sup>1</sup> *Pneumocystis* was described as a protozoan in older literature.<sup>14</sup> Pneumocystosis is rarely detected in healthy people, but up to approximately 70% of HIV-infected people have *P jirovecii* in their respiratory tract.<sup>15</sup> Almost all of the cases of pneumocystosis are in individuals with AIDS or with long-term immunosuppression. *Pneumocystis* pneumonia (PCP) was the defining opportunistic disease for two-thirds of AIDS patients in the United States during the onset of the AIDS pandemic.<sup>15</sup> The PCP-related fatalities in the USAF are consistent with the trends for the AIDS pandemic. Approximately one-third of deaths occurred in each decade. The first 2 pneumocystosis deaths in our study were reported in 1986, and there were 7 deaths total in that decade. There were 25 deaths in patients ranging in age from 35 to 80 years. The majority of deaths (n=13) occurred in the 1990s, with 5 deaths recorded since 2000. The most recently recorded pneumocystosis death in the AFMR was in 2012.

Advances in antiretroviral drugs have greatly extended the lifespan and health of individuals infected with HIV. There were no female deaths recorded for pneumocystosis. All subjects with this underlying cause of death in our review were retired.

**Sporotrichosis:** This disease is caused by *Sporothrix schenckii*, and most infections are opportunistic, self-limiting, and cutaneous.<sup>16</sup> The primary route of infection is through cuts from fungus-contaminated wires, thorns, needles, etc. Among the fungal causes of death in the AFMR, sporotrichosis was the least common. Two deaths of retirees were recorded, with one disseminated infection and one that was unspecified in terms of body organ/region affected. Both men were aged in their 60s. Additional information was not available, but presumably they had compromised immune systems.

**Unspecified Mycosis:** Unspecified mycosis tied with candidiasis for the greatest number of deaths. While we do not have enough information on the deceased, a specific fungal agent was not investigated postmortem. Unspecified mycosis deaths contribute almost 20% of our data, with 43 deaths. The death of a 52-year-old male active duty member resulted from an unspecified mycosis; the remainder were retirees. Two of the 4 women in our review died from unspecified mycosis.

Based on the death records, the threat of fungal diseases to active duty Airmen is very low, and fatal cases are extremely rare. Women die less frequently from fungal infections, but are a smaller component of the military overall.

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### REFERENCES

1. Reeves WK, Bettano AL. A review of mortality from parasitic and vector-borne diseases in the US Air Force from 1970 to 2012. *J Parasitol.* 2014;100(2):189-192.
2. Anna MM, Escobar JD, Chapman AS. Reported vectorborne and zoonotic diseases, U.S. Air Force, 2000-2011. *MSMR.* 2012;61(10):11-12; discussion 12-14.
3. Latgé JP. *Aspergillus fumigatus* and aspergillosis. *Clin Microbiol Rev.* 1999;12(2):310-350.



4. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis*. 2001;32(3):358-366.
5. Centers for Disease Control and Prevention. Blastomycosis--Wisconsin, 1986-1995. *MMWR Morb Mortal Wkly Rep*. 1996;45(28):601-603.
6. Hughes WT. Systemic candidiasis: a study of 109 fatal cases. *Pediatr Infect Dis*. 1982;1(1):11-18.
7. Standaert SM, Schaffner W, Galgiani JN, et al. Coccidioidomycosis among visitors to a Coccidioides immitis-endemic area: an outbreak in a military reserve unit. *J Infect Dis*. 1995;171(6):1672-1675.
8. MacDougall L, Kidd SE, Galanis E, et al. Spread of *Cryptococcus gattii* in British Columbia, Canada, and detection in the Pacific Northwest, USA. *Emerg Infect Dis*. 2007;13(1):42-50.
9. Park BJ, Wannemuehler KA, Marston BJ, et al. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS*. 2009;23(4):525-530.
10. Kwon-Chung KJ. Studies on *Emmonsia capsula* I. Heterothallism and development of the ascocarp. *Mycologia*. 1973;65(1):109-121.
11. Baddley JW, Winthrop KL, Patkar NM, et al. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis*. 2011;17(9):1664-1669.
12. Etienne KA, Gillece J, Hilsabeck R, et al. Whole genome sequence typing to investigate the *Apophysomyces* outbreak following a tornado in Joplin, Missouri. *PloS One*. 2011;7(11):e49989.
13. Gomes MZR, Lewis RE, Kontoyiannis DP. Murcomycosis caused by unusual mucormycetes, non-*Rhizopus*, *Mucor*, and *Lichtheimia* species. *Clin Microbiol Rev*. 2011;24(2):411-45.
14. Feeney KT, Arthur IH, Whittle AJ, et al. Outbreak of sporotrichosis, Western Australia. *Emerg Infect Dis*. 2007;13(8):1228-1231.
15. Morris SK, Brophy J, Richardson SE, et al. Blastomycosis in Ontario, 1994-2003. *Emerg Infect Dis*. 2006;12(2):274-279.
16. James TY, Kauff F, Schoch CL, et al. Reconstructing the early evolution of fungi using a six-gene phylogeny. *Nature*. 2006;443(7113):818-822.

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